REMARKS

Applicants wish to thank Examiner Popa for the courtesies extended during an interview with the undersigned on October 16, 2007. The interview attempted to clarify issues relating to the May 2, 2007 Office Action rejections. As discussed with the Examiner, Applicants have amended claim 1 to recite detection of quantitative PCR products and have supplied further data showing that Taq is not inactivated by foam.

Claims 1-4, 7-18 and 21-22 are pending in the application. Claims 2 and 4 have been canceled, claims 1, 3, 5, 7-8 and 11 have been amended. Claims 5-6 and 19-20 are currently withdrawn from consideration. Claim 22 has been added. The amendments to the claims and the added claims are fully supported by the original claims and specification. Claims 1 and 11 have been amended to add elements previously recited in dependent claims. Claims 3, 5, and 7 have been amended to correct dependencies and claim 8 has been amended to correct a grammatical inconsistency. Claim 22 finds support in the specification at least on page 13, lines 29-31 and page 17, lines 7-8.

In the May 2, 2007 Office Action, claims 1, 11, 12, 22, and 23 were rejected under 35 U.S.C. § 102(b) as anticipated by Stemmer et al. (U.S. Patent No. 5,834,252), as evidenced by Maa et al. (*Biotechnology and Bioengineering*, 1997, 54:503-512) and Takahashi et al. (*Sci SRKE*, 2000, 56: p11). Claims 1-4, 7, 11, 15-18, and 21-23 were rejected under 35 U.S.C. § 103(a) as unpatentable over Blaschke et al. (*J. Immunol. Methods*, 2000, 246: 79-90, of record), in view of 1) Stemmer taken with Maa et al. and Takahashi et al., 2) Varadaraj et al. (*Gene* 1994, 140:1-5, Abstract), and 3) Swedlow et al. (*Anal. Chem.*, 1997, 69: 848-855). Claims 1, 9, 11-13 and 22-23 were rejected under 35 U.S.C. § 103(a) as unpatentable over Stemmer et al. taken with Maa et al. and Takahashi et al., in further view of Kyle (U.S. Patent No. 5,658,787, of record). Claims 1, 8-14 and 22-23 were rejected under 35 U.S.C. §103(a) as unpatentable over Stemmer et al. taken with Maa et al., Takahashi et al., and Kyle, in further view of Sigma catalog (1998) and Wieranga (U.S. Patent No. 5,968,889). The specific grounds for rejection, and applicants' response thereto, are set forth in detail below.

Rejections Under 35 U.S.C. §102

Claims 1, 11, 12, 22, and 23 are rejected under 35 U.S.C. § 102(b) as anticipated by Stemmer et al. (U.S. Patent No. 5,834,252), as evidenced by Maa et al. (*Biotechnology and Bioengineering*, 1997, 54:503-512) and Takahashi et al. (*Sci SRKE*, 2000, 56: pl1). Applicants respectfully traverse.

It is axiomatic that, for a prior art reference to be anticipatory, every element of the claimed invention must be identically shown in a single reference. *In re Bond*, 15 U.S.P.Q. 2d 1566 (Fed. Cir. 1990). Stemmer fails to disclose all the limitations of the instantly claimed invention. More specifically, Stemmer is silent regarding optical detection of a quantitative polymerase chain reaction. Accordingly, Stemmer fails to anticipate the instantly claimed invention and the rejection should be withdrawn.

Applicants previously submitted a declaration by Mark Berninger ("Berninger") that explained the deficiencies of Stemmer as an anticipatory reference. Applicants incorporate Berninger In seeking to rebut Berninger the Examiner states that the prior art teaches

> (i) that proteins in general and Taq polymerase in particular are inactivated by foam and (ii) the use of antifoam agents to prevent denaturation of proteins by foaming

At the October 16, 2007 interview applicants explained that, whether or not this was true for some proteins, it is not true for the types of polymerase used in the polymerase chain reaction. Appended hereto is a declaration from one of the inventors of the instant application, Dr. Ayoub Rashtchian, describing experiments that show that *Taq* polymerase, the most commonly used polymerase for PCR, is not inactivated by foam.

Rejections Under 35 U.S.C. §103(a)

Claims 1-4, 7, 11, 15-18, and 21-23 were rejected under 35 U.S.C. § 103(a) as unpatentable over Blaschke et al. (*J. Immunol. Methods*, 2000, 246: 79-90, of record), in view of 1) Stemmer taken with Maa et al. and Takahashi et al., 2) Varadaraj et al. (*Gene* 1994, 140:1-5, Abstract), and 3) Swedlow et al. (*Anal. Chem.*, 1997, 69: 848-855). Claims 1, 9, 11-13 and 22-23 were rejected under 35 U.S.C. § 103(a) as unpatentable over Stemmer et al. taken with Maa et al. and Takahashi et al., in further view of Kyle (U.S. Patent No. 5,658,787, of record). Claims 1, 8-14 and 22-23 were rejected under 35 U.S.C. §103(a) as unpatentable over Stemmer et al.

taken with Maa et al., Takahashi et al., and Kyle, in further view of Sigma catalog (1998) and Wieranga (U.S. Patent No. 5,968,889). Applicants respectfully traverse.

At the outset, applicants reassert and incorporate their arguments of record, namely that the combinations proposed by the Examiner fail to establish *prima facie* obviousness. In brief, the Examiner asserts that Blaschke teaches real-time RT-PCR methods but does not teach use of detergents or anti-foam reagents. Stemmer is cited as providing the motivation to add detergents and antifoam reagents Varadaraj is cited as teaching that detergents improve the specificity of the amplification process. Swerdlow is cited as teaching that air bubbles interfere with microfluidic technology and that detergents create air bubbles.

In citing the above art references, the Examiner picks and chooses from the disclosures only so much as to support her obviousness rejection. This type of "cherry picking" is improper as the Federal Circuit has stated:

> [i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art. (*Bausch & Lomb, Inc., v. Barnes-Hind/Hydrocurve, Inc.*, 796, F.2d 443, 448 (Fed. Cir. 1986) (quoting *In re Wesslau*, 355 F. 2d 238, 241 (CCPA 1965)).

For example, Varadaraj may suggest that in certain circumstances certain detergents may be added to a PCR, but it also states that ethanol *inhibited* PCR amplification. The Examiner previously has stated that ethanol is an antifoam. Following the Examiner's reasoning one of ordinary skill in the art would have concluded that addition of an antifoam would inhibit PCR and would therefore would not have been motivated to add an antifoam to a PCR reaction. This disclosure in Varadaraj *must* be taken into account when assessing whether or not the instantly claimed invention is obvious and obviates any case of *prima facie* obviousness using this reference. Indeed, Varadaraj's teaching that PCR was inhibited with ethanol actually teaches away from the instantly claimed invention. It is impermissible to combine references where a reference teach away from the combination. See MPEP 2145.

Blaschke is cited as teaching real time PCR methods but fails to teach use of detergents or antifoam. However, nothing in Blaschke would suggest to one or ordinary skill in the art that *anything* need be added to a real time PCR reaction other than the reagents described by Blaschke. Thus, Blaschke specifically describes obtaining single band PCR products (see page

83, right hand column) and fails to teach or suggest that any improvement to the PCR protocols is necessary. If a single band product already is obtained, why would one of ordinary skill in the art be motivated to try to improve a specificity that already is optimal? Nothing in the cited art suggests that any improvement is necessary, so no motivation exists to modify Blaschke by adding detergents as described by Varadaraj.

Nothing in Stemmer teaches or describes quantitative PCR, as recited in the instant claims. Moreover, Stemmer must be considered for all that it teaches, not merely any part of the reference that supports the Examiner's assertions regarding obviousness. In particular, as previously described in Berninger, Stemmer suggests use of conditions that are incompatible with either PCR or quantitative PCR. One of ordinary skill in the art reading Stemmer clearly would recognize this incompatibility and would not be motivated by any alleged teachings regarding PCR.

Swerdlow is cited as teaching that air bubbles interfere with microfluidic technology and can be removed using a chromatography column. However, the source of the bubbles is a mystery. With respect, applicants query why, if it was obvious to use an antifoam in a PCR reaction, did Swerdlow go to the great effort of using a chromatography column to eliminate the mystery bubbles? Chromatography is a significantly more onerous procedure to use as compared to adding antifoam. The inescapable conclusion is that it was not obvious to Swerdlow, let alone one of ordinary skill in the art, to use an antifoam in a PCR reaction.

Finally, in the event that the Examiner seeks to maintain that a *prima facie* case of obviousness exists despite the manifold deficiencies of the cited reference, applicants submit that any evidence of obviousness is rebutted by the surprising results described in applicants' specification. Specifically, applicants' specification shows that the instantly claimed methods surprisingly allows detection measurements that are free of artifacts. For example, FIGS 2 and 4 of the instant specification illustrate the deleterious effect of foaming on threshold cycle (Ct) determination in real-time PCR from identical reactions containing 20 copies of template DNA per reaction. The only difference between the two reactions is the inclusion of antifoam in the reactions recorded in FIG 4. FIG 2 shows that fluorescence readings were distorted with respect to baseline and Ct determinations in qPCR reactions without the addition of anti-foaming agents. Specifically the bubble error in wells H1 to H6 resulted in Ct values ranging from 33 to 38, which represents approximately a 15 fold difference. FIG 4, however, surprisingly shows that

the addition of anti-foam not only limited bubble formation, but produced a stable baseline allowing for a more accurate reading. The greatest variation in these antifoam containing tests was 1 Ct, which represent approximately a 2 fold difference in quantification.

The secondary references are cited only to show that specific antifoam reagents were known and might, under certain circumstances, be used in combination. Accordingly, the secondary references fail to remedy the deficiencies of the primary references as set forth above.

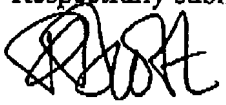
In sum, applicants respectfully submit that the Examiner has failed to present a *prima facie* case of obviousness. Moreover, even if, for the sake of argument only, it is assumed that a *prima facie* case of obviousness exists, the evidence of surprising results as described above, negates such *prima facie* case. Accordingly, withdrawal of the rejection respectfully is requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the application is in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-3840. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).**

Respectfully submitted,



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